

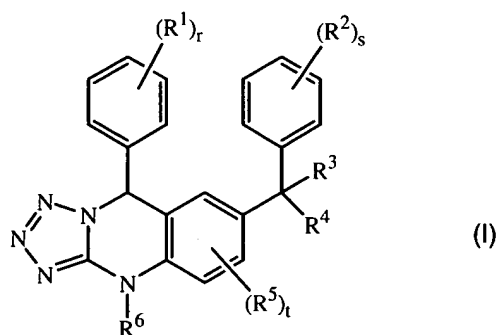
Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

Claims 1-10 (canceled)

Claims

11. A compound of formula (I):



or a pharmaceutically acceptable salt or N-oxide or stereochemically isomeric form thereof, wherein

r and s are each independently 0, 1, 2 or 3;

t is 0, 1, or 2;

each R^1 and R^2 are independently hydroxy, halo, cyano, nitro, C_{1-6} alkyl, $-(CR^{16}R^{17})_p$, $-C_{3-10}$ cycloalkyl, cyano C_{1-6} alkyl, hydroxy C_{1-6} alkyl, C_{1-6} alkyloxy C_{1-6} alkyl, hydroxycarbonyl C_{1-6} alkyl, $R^{20}SC_{1-6}$ alkyl, trihalomethyl, aryl C_{1-6} alkyl, Het¹ C_{1-6} alkyl, $-C_{1-6}$ alkyl- $NR^{18}R^{19}$, $-C_{1-6}$ alkyl- $NR^{18}C_{1-6}$ alkyl- $NR^{18}R^{19}$, $-C_{1-6}$ alkyl- $NR^{18}COC_{1-6}$ alkyl, $-C_{1-6}$ alkyl- $NR^{18}COAlkAr^1$, $-C_{1-6}$ alkyl- $NR^{18}COAr^1$, C_{1-6} alkylsulphonylamino C_{1-6} alkyl, C_{1-6} alkyloxy, hydroxy C_{1-6} alkyloxy, C_{1-6} alkyloxy C_{1-6} alkyloxy, $-OC_{1-6}$ alkyl- $NR^{18}R^{19}$, trihalomethoxy, aryl C_{1-6} alkyloxy, Het¹ C_{1-6} alkyloxy, C_{2-6} alkenyl, cyano C_{2-6} alkenyl, $-C_{2-6}$ alkenyl- $NR^{18}R^{19}$, hydroxycarbonyl C_{2-6} alkenyl,

C₁₋₆alkyloxycarbonylC₂₋₆alkenyl, C₂₋₆alkynyl, -CHO, C₁₋₆alkylcarbonyl, hydroxyc₁₋₆alkylcarbonyl, hydroxycarbonyl, C₁₋₆alkyloxycarbonyl,
 -CONR¹⁸R¹⁹, -CONR¹⁸-C₁₋₆alkyl-NR¹⁸R¹⁹, -CONR¹⁸-C₁₋₆alkyl-Het¹,
 -CONR¹⁸-C₁₋₆alkyl-Ar¹, -CONR¹⁸-O-C₁₋₆alkyl, -CONR¹⁸-C₁₋₆alkenyl,
 -NR¹⁸R¹⁹, -OC(O)R²⁰, -CR²⁰=NR²¹, -CR²⁰=N-OR²¹, -NR²⁰C(O)NR¹⁸R¹⁹,
 -NR²⁰SO₂R²¹, -NR²⁰C(O)R²¹, -S-R²⁰, -S(O)-R²⁰, -S(O)₂R²⁰, -SO₂NR²⁰R²¹,
 -C(NR²²R²³)=NR²⁴,

or a group of formula



in which R^Y is hydrogen or C₁₋₄alkyl and Z is phenyl or a 5- or 6-membered heterocyclic ring containing one or more heteroatoms selected from oxygen, sulphur and nitrogen, the phenyl or heterocyclic ring being optionally substituted by one or two substituents each independently selected from halo, cyano, hydroxycarbonyl, aminocarbonyl, C₁₋₆alkylthio, hydroxy, -NR¹⁸R¹⁹,

C₁₋₆alkylsulphonylamino, C₁₋₆alkyl, haloC₁₋₆alkyl, C₁₋₆alkyloxy or phenyl; or two R¹ and R² substituents adjacent to one another on the phenyl ring may independently form together a bivalent radical of formula

- O-CH₂-O- (a-1)
- O-CH₂-CH₂-O- (a-2)
- O-CH=CH- (a-3)
- O-CH₂-CH₂- (a-4) or
- O-CH₂-CH₂-CH₂- (a-5)

R¹⁶ and R¹⁷ are independently hydrogen or C₁₋₆ alkyl;
 R¹⁸ and R¹⁹ are independently hydrogen, C₁₋₆ alkyl or
 -(CR¹⁶R¹⁷)_p-C₃₋₁₀cycloalkyl, or together with the adjacent nitrogen atom form a 5- or 6-membered heterocyclic ring optionally containing one, two or three further heteroatoms selected from oxygen, nitrogen or sulphur and optionally substituted by one or two substituents each independently selected from halo, hydroxy, cyano, nitro, C₁₋₆alkyl, haloC₁₋₆alkyl, C₁₋₆alkyloxy, OCF₃, hydroxycarbonyl, C₁₋₆alkyloxycarbonyl, aminocarbonyl,

mono- or di-(C₁₋₆alkyl)aminocarbonyl, amino, mono- or di(C₁₋₆alkyl)amino, C₁₋₆alkylsulfonylamino, oxime, or phenyl;
R²⁰ and R²¹ are independently hydrogen, C₁₋₆alkyl, -(CR¹⁶R¹⁷)_p-C₃₋₁₀cycloalkyl or arylC₁₋₆alkyl;
R²², R²³ and R²⁴ are independently hydrogen and C₁₋₆alkyl or C(O) C₁₋₆alkyl;
p is 0 or 1;

R³ is hydrogen, halo, cyano, C₁₋₆alkyl, -(CR¹⁶R¹⁷)_p-C₃₋₁₀cycloalkyl, haloC₁₋₆alkyl, cyanoC₁₋₆alkyl, hydroxyC₁₋₆alkyl, C₁₋₆alkyloxyC₁₋₆alkyl, arylC₁₋₆alkyloxy C₁₋₆alkyl, C₁₋₆alkylthioC₁₋₆alkyl, hydroxycarbonylC₁₋₆alkyl, C₁₋₆alkylcarbonyl C₁₋₆alkyl, C₁₋₆alkyloxycarbonylC₁₋₆alkyl, -C₁₋₆alkyl-NR¹⁸R¹⁹, -C₁₋₆alkyl-CONR¹⁸R¹⁹, arylC₁₋₆alkyl, Het¹C₁₋₆alkyl, C₂₋₆alkenyl, -C₂₋₆alkenyl NR¹⁸R¹⁹, C₂₋₆alkynyl, hydroxycarbonyl, C₁₋₆alkyloxycarbonyl, aryl, or Het¹; or a radical of formula



wherein R⁷ is hydrogen, C₁₋₆alkyl, -(CR¹⁶R¹⁷)_p-C₃₋₁₀cycloalkyl, arylC₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkylcarbonyl or -C₁₋₆alkylC(O)OC₁₋₆alkyl NR¹⁸R¹⁹, or a radical of formula -Alk-OR¹⁰ or -Alk-NR¹¹R¹²;

R⁸ is hydrogen, C₁₋₆alkyl, -(CR¹⁶R¹⁷)_p-C₃₋₁₀cycloalkyl, C₂₋₆alkenyl or C₂₋₆alkynyl;

R⁹ is hydrogen, hydroxy, C₁₋₆alkyl, -(CR¹⁶R¹⁷)_p-C₃₋₁₀cycloalkyl, C₁₋₆alkylcarbonylC₁₋₆alkyl, arylC₁₋₆alkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, aryl, C₁₋₆alkyloxy, a group of formula -NR¹⁸R¹⁹, C₁₋₆alkylcarbonylamino, C₁₋₆alkylcarbonyl, haloC₁₋₆alkylcarbonyl, arylC₁₋₆alkylcarbonyl, arylcarbonyl, C₁₋₆alkyloxycarbonyl, trihaloC₁₋₆alkyloxycarbonyl, C₁₋₆alkyloxyC₁₋₆alkylcarbonyl, aminocarbonyl, mono-

or di(C₁₋₆alkyl)aminocarbonyl wherein the alkyl moiety may optionally be substituted by one or more substituents independently selected from aryl and C₁₋₆alkyloxycarbonyl substituents; aminocarbonylcarbonyl, mono- or di(C₁₋₆alkyl)aminoC₁₋₆alkylcarbonyl, or a radical of formula -Alk-OR¹⁰ or Alk-NR¹¹R¹²;

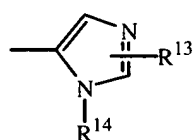
wherein Alk is C₁₋₆alkanediyl;

R¹⁰ is hydrogen, C₁₋₆alkyl, -(CR¹⁶R¹⁷)_p-C₃₋₁₀cycloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkylcarbonyl or hydroxyc₁₋₆alkyl;

R¹¹ is hydrogen, C₁₋₆alkyl, -(CR¹⁶R¹⁷)_p-C₃₋₁₀cycloalkyl, C₂₋₆alkenyl or C₂₋₆alkynyl;

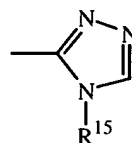
R¹² is hydrogen, C₁₋₆alkyl, -(CR¹⁶R¹⁷)_p-C₃₋₁₀cycloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl or C₁₋₆alkylcarbonyl;

R⁴ is a radical of formula



(c-1)

or



(c-2)

wherein R¹³ is hydrogen, halo or C₁₋₆alkyl;

R¹⁴ is hydrogen or C₁₋₆alkyl;

R¹⁵ is hydrogen or C₁₋₆alkyl;

R⁵ is cyano, hydroxy, halo, C₁₋₆alkyl, -(CR¹⁶R¹⁷)_p-C₃₋₁₀cycloalkyl, C₂₋₆alkenyl, C₂₋₆alkynyl, C₁₋₆alkyloxy, hydroxycarbonyl, C₁₋₆alkyloxycarbonyl, or a group of formula -NR¹⁸R¹⁹ or -CONR¹⁸R¹⁹;

R⁶ is hydrogen, C₁₋₆alkyl, -(CR¹⁶R¹⁷)_p-C₃₋₁₀cycloalkyl, cyanoC₁₋₆alkyl, -C₁₋₆alkylCO₂R²⁰, aminocarbonylC₁₋₆alkyl, -C₁₋₆alkyl-NR¹⁸R¹⁹, R²⁰SO₂, R²⁰SO₂C₁₋₆alkyl, -C₁₋₆alkyl-OR²⁰, -C₁₋₆alkyl-SR²⁰, -C₁₋₆alkylCONR¹⁸-C₁₋₆alkyl-NR¹⁸R¹⁹, -C₁₋₆alkylCONR¹⁸-C₁₋₆alkyl-Het¹, -C₁₋₆alkylCONR¹⁸-C₁₋₆alkyl-Ar¹, -C₁₋₆alkylCONR¹⁸-Het¹, -C₁₋₆alkylCONR¹⁸Ar¹, -C₁₋₆alkylCONR¹⁸-O-C₁₋₆alkyl,

-C₁₋₆alkylCONR¹⁸-C₁₋₆alkenyl, -Alk-Ar¹ or -AlkHet¹;

Ar¹ is phenyl, naphthyl or phenyl or naphthyl substituted by one to five substituents each independently selected from halo, hydroxy, cyano, nitro, C₁₋₆alkyl, haloC₁₋₆alkyl, -alkylNR¹⁸R¹⁹, C₁₋₆alkyloxy, OCF₃, hydroxycarbonyl, C₁₋₆alkyloxycarbonyl, -CONR¹⁸R¹⁹, -NR¹⁸R¹⁹, C₁₋₆alkylsulfonylamino, oxime, phenyl, or a bivalent substituent of formula

-O-CH₂-O- or

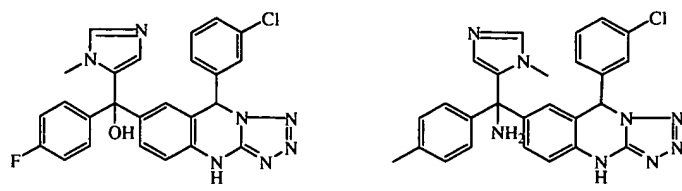
-O-CH₂-CH₂-O-;

Het¹ is a mono- or bi-cyclic heterocyclic ring containing one or more heteroatoms selected from oxygen, sulphur and nitrogen and optionally substituted by one or two substituents each independently selected from halo, hydroxy, cyano, nitro, C₁₋₆alkyl, haloC₁₋₆alkyl, -alkylNR¹⁸R¹⁹, C₁₋₆alkyloxy, OCF₃, hydroxycarbonyl, C₁₋₆alkyloxycarbonyl, -CONR¹⁸R¹⁹, -NR¹⁸R¹⁹, C₁₋₆alkylsulfonylamino, oxime or phenyl.

12. A compound according to claim 11 wherein r is 1, s is 1 and t is 0; R¹ is halo; R² is halo, C₁₋₆alkyl, C₁₋₆alkyloxy or C₁₋₆alkyloxycarbonyl; R³ is hydrogen or a radical of formula (b-1) or (b-3) wherein R⁷ is hydrogen or C₁₋₆alkyl, R⁸ is hydrogen and R⁹ is hydrogen; R⁴ is a radical of formula (c-1) or (c-2) wherein R¹³ is hydrogen, R¹⁴ is C₁₋₆alkyl and R¹⁵ is C₁₋₆alkyl; and R⁶ is hydrogen, C₁₋₆alkyl, -(CH₂)_p-C₃₋₁₀cycloalkyl, -C₁₋₆alkylCO₂C₁₋₆alkyl or -Alk-Ar¹.

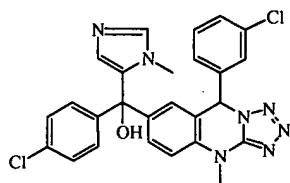
13. A compound according to claim 11 wherein r is 1, s is 1 and t is 0; R¹ is halo; R² is halo, C₁₋₆alkyl or C₁₋₆alkyloxy; R³ is hydrogen, hydroxy or amino; R⁴ is a radical of formula (c-1) wherein R¹³ is hydrogen and R¹⁴ is C₁₋₆alkyl; and R⁶ is hydrogen or C₁₋₆alkyl.

14. A compound according to claim 11 selected from the following compounds No 2, No 5, No 19, No 20 and No 23.

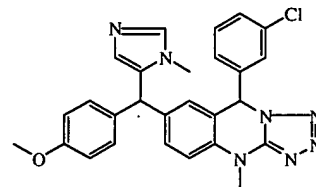


compound 2

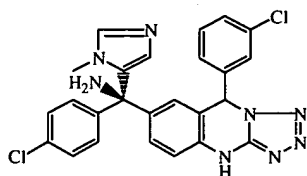
compound 5



compound 19



compound 20



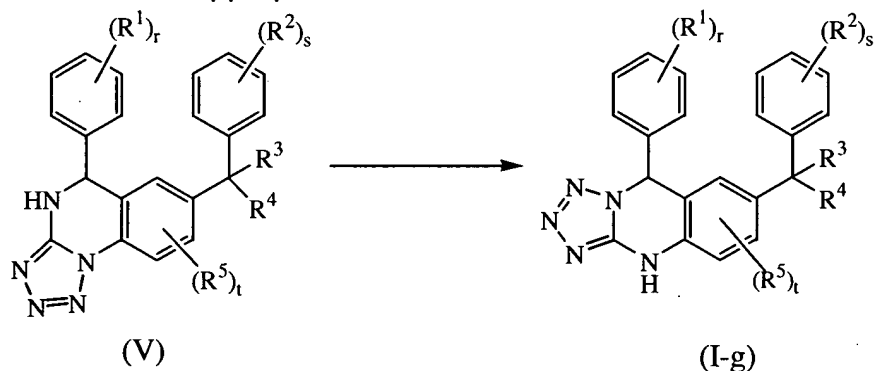
compound 23.

15. A pharmaceutical composition comprising pharmaceutically acceptable carriers and as an active ingredient a therapeutically effective amount of a compound as claimed in claim 11.
16. A process of preparing a pharmaceutical composition as claimed in claim 15 wherein the pharmaceutically acceptable carriers and the compound are intimately mixed.
17. The method of treating proliferative disorders comprising administering to a patient in need of such treatment, an anti-proliferative disorder-effective amount of a compound of Claim 11.

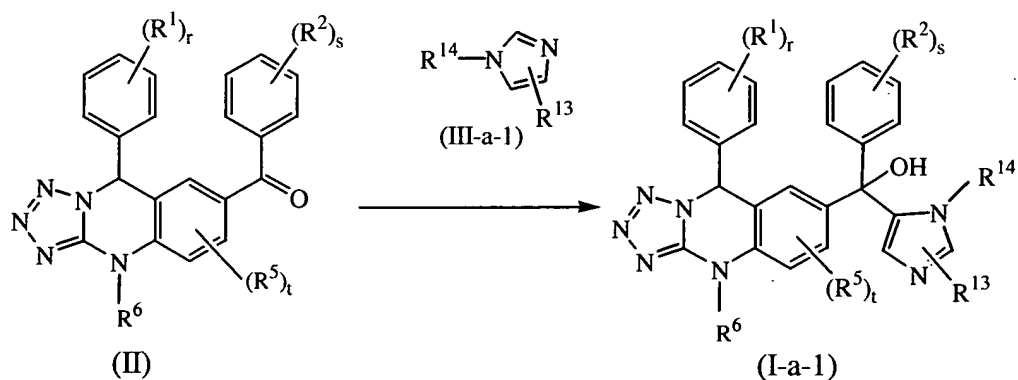
18. The method of inhibiting tumor growth comprising administering to a patient in need of such treatment, an anti- inhibiting tumor growth -effective amount of a compound of Claim 11.

19. A process for the preparation of a compound as claimed in claim 11 which comprises:

a) Converting intermediates of formula (V) in compounds of formula (I) wherein R⁶ is hydrogen said compounds being referred to as compounds of formula (I-g) by heating at 120 °C in an appropriate solvent; and

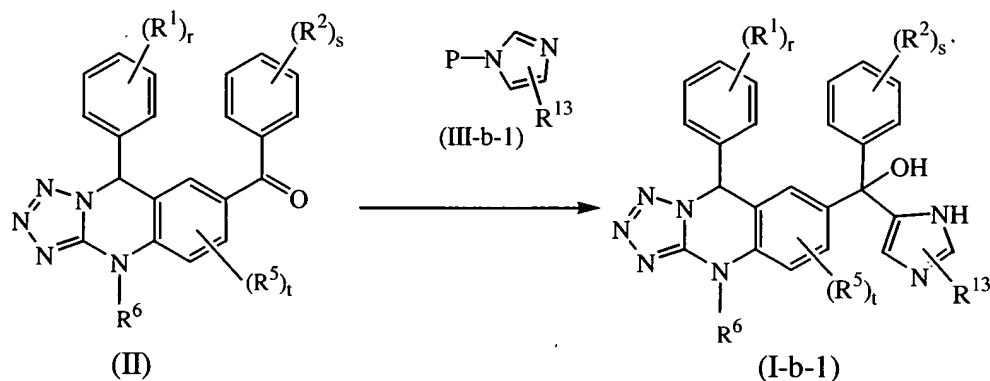


b) reacting an intermediate ketone of formula (II) with an intermediate imidazole of formula (III-a-1) wherein R¹⁴ is C₁₋₆alkyl with the formation of compounds of formula (I) wherein R⁴ represents a radical of formula (c-1), R³ is hydroxy and R¹⁴ is C₁₋₆alkyl, said compounds being referred to as compounds of formula (I-a-1); and



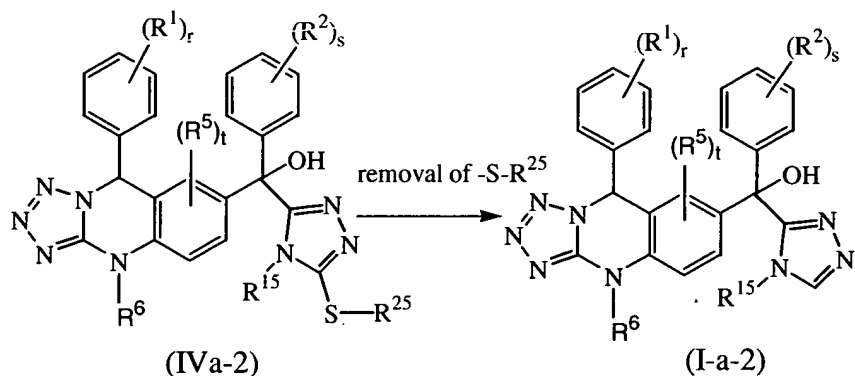
c) reacting an intermediate ketone of formula (II) with an intermediate imidazole reagent of formula (III-b-1) wherein P is an optional protective group and R¹⁴ is

hydrogen and subsequently removal of P with the formation of a compound of formula (I) wherein R^4 is a radical of formula (c-1), R^3 is hydroxy and R^{14} is hydrogen said compound being referred to as compounds of formula (I-b-1); and

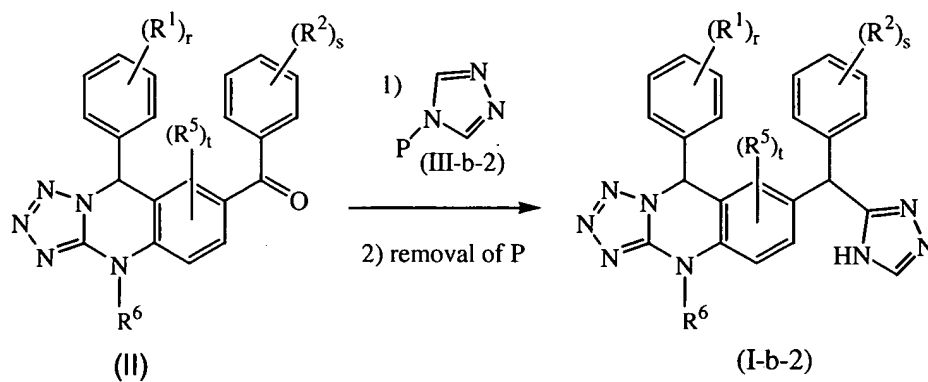


d) removing the $-S-R^{25}$ group, wherein R^{25} is hydrogen or C_{1-6} alkyl from the intermediate of formulae (IVa-2) wherein R^4 is a radical of formula

(c-2), R^{15} is C_{1-6} alkyl and R^3 is hydroxy with the formation of compounds of formula (I), wherein R^4 is a radical of formula (c-2), R^{15} is C_{1-6} alkyl and R^3 is hydroxy, said compounds being referred to as compounds of formula (I-a-2); and



e) reacting an intermediate ketone of formula (II) with an intermediate triazole reagent of formula (III-b-2) wherein P is an optional protective group and subsequently removal of P with the formation of a compound of formula (I) wherein R^4 is a radical of formula (c-2), R^3 is hydroxy and R^{14} is hydrogen said compound being referred to as compounds of formula (I-b-2) ; and



f) optionally effecting one or more of the following conversions in any desired order:

- (i) converting a compound of formula (I) into a different compound of formula (I);
- (ii) converting a compound of formula (I) into a pharmaceutically acceptable salt or N-oxide thereof;
- (iii) converting a pharmaceutically acceptable salt or N-oxide of a compound of formula (I) into the parent compound of formula (I);
- (iv) preparing a stereochemical isomeric form of a compound of formula (I) or a pharmaceutically acceptable salt or N-oxide thereof.